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Synthesis and photocleavage of a new dimeric bis(*o*-nitrobenzyl) diether tether†

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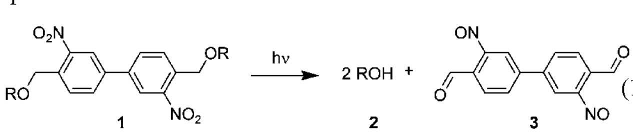
A new photocleavable linker, 4,4′-bis(alkoxymethyl-3,3′-dinitro)biphenyl, is reported that undergoes photolysis at two positions to release two equivalents of primary, secondary, or benzylic alcohol in yields that are higher than those obtained from the analogous monomeric *o*-nitrobenzyl ethers.

The development of molecular switches that undergo a distinct change in the presence of well-defined signals is an area of intense research, with potential applications in sensing, molecular electronics, and artificial signal transduction.[1] Among the signals investigated, light is of particular interest because of its selectivity for specific chromophores, and the ease with which it is applied to the substrate. The use of light to trigger homolytic bond cleavage has been applied to the study of protein folding,[2] and light-induced photoisomerization has been shown to trigger changes in supramolecular association.[3]

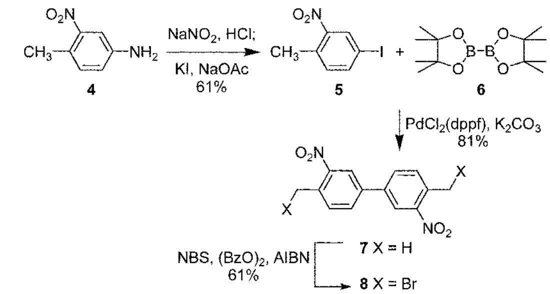
We are interested in using light to trigger the release of two alcohols in close proximity. Photocleavable linkers have gained widespread use in solid phase synthesis for attachment of target compounds to a polymeric support.[4] The photoreactive functionalities are inert to most reaction conditions, but cleanly undergo photolysis upon irradiation to release the product. For solid phase photocleavable linkers, the by-product of the photolytic reaction remains attached to the polymeric support. Despite the potential utility of a photochemically excised tether, examples in which a linker is cleaved at two positions are scarce. Kutateladze and coworkers have developed dithiane scaffolds that can release two carbonyl functional groups upon electron-transfer sensitized photodeprotection,[5] and Taylor has reported the use of an *ortho*-nitrobenzyl dimer linked at the benzylic positions to tether DNA strands *via* the 3′- and 5′-phosphates in order to study DNA strand scission repair.[6]

Toward our goal of an excisable photocleavable linker, *ortho*-nitrobenzyl ether dimer **1** was designed in which the two aromatic rings are directly linked to form a rigid tether (eqn. (1)). Photolysis would result in the formation of two equivalents of alcohol **2** and the bis(nitrosoaldehyde) by-product **3**. The corresponding *o*-nitrobenzyl ether monomer is a well-known photocleavable protecting group,[7] and analogs of the monomer have been used in a number of applications involving photolytic release of a compound of interest.[8] However, biaryl dimers of *o*-nitrobenzyl ethers have not been previously reported, and it was not clear what effect the extended conjugation would have on the photochemistry of the *o*-nitrobenzyl group. Thus we set out to prepare such ethers and test their viability as completely excisable bifunctional photocleavable linkers.



(1)

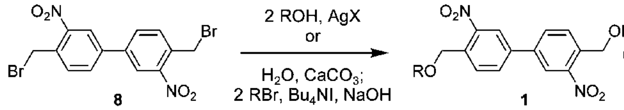
In order to prepare diethers **1**, we first needed to prepare the precursor, bis(*o*-nitrobenzyl) dibromide **8** (Scheme 1). Thus,



Scheme 1 Synthesis of dibromide **8**.

commercially available *m*-nitrotoluidine (**4**) was converted to the aromatic iodide **5** in 61% yield by nitrous acid mediated generation of the diazonium salt followed by treatment with potassium iodide. The aromatic iodide **5** was then subjected to Suzuki coupling conditions with bis(pinacolato)diboron (**6**), catalytic $PdCl_2$(dppf) and potassium carbonate in order to furnish 4,4′-dimethyl-3,3′-dinitro biphenyl (**7**) in 81% yield.[9] Biaryl **7** was then subjected to radical bromination at the benzylic positions using *N*-bromosuccinimide (NBS) and a mixture of benzoyl peroxide and 2,2′-azobisisobutyronitrile (AIBN) to furnish dibromide **8** (61%).

With the new bifunctional protecting group **8** in hand, we set out to prepare diethers **1a–e** in order to investigate the photochemistry of the dimeric *o*-nitrobenzyl group. Toward this end, we prepared ethers of primary alcohols serinol **2a**, *n*-hexadecanol **2b**, *n*-propanol **2c**, and secondary cyclohexanol **2d**, using silver salts to activate the benzylic bromide (eqn. (2)). Dibenzyl ether **1e** was prepared under basic phase-transfer conditions (see ESI for details†). The corresponding monomeric *o*-nitrobenzyl ethers **9**, derived from commercially available *o*-nitrobenzyl bromide, were also prepared for comparison.



(2)

At the outset, it was not known whether the conjugated biaryl dimer **1** would undergo photolysis in the same manner as the monomeric *o*-nitrobenzyl ether, as it was not clear what effect the extended conjugation would have on the photochemistry of the ring system. Thus once diethers **1** and monoethers **9** were prepared, deoxygenated benzene solutions of the ethers were irradiated using a Rayonet Photochemical Reactor equipped with bulbs emitting at λ_{max} = 350 nm (Table 1). All substrates were irradiated for 2 hours for the sake of comparison. We were pleased to discover that the yield of alcohol recovered from the photolysis of dimeric ethers **1** was superior to that of the analogous monomers **9** in all cases. The highest yield of recovered alcohols was observed for relatively large, hydrophobic primary alcohols **2a** and **2b** (entries 1 and 2) which were isolated in quantitative yields following purification by silica gel column chromatography.

Because of the volatility of *n*-propanol (**2c**, entry 3), cyclohexanol (**2d**, entry 4) and benzyl alcohol (**2e**, entry 5), purification of the alcohol products resulted in some loss due to evaporation of the

† Electronic supplementary information (ESI) available: experimental procedures and spectral characterization. See http://www.rsc.org/suppdata/cc/b4/b408482a/

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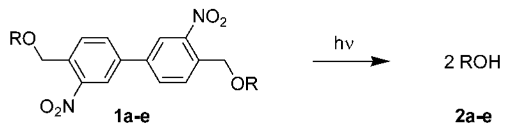
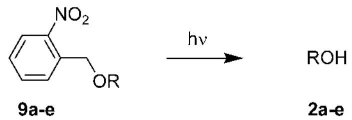
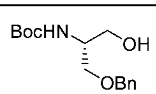
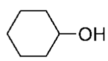
Table 1 Photocleavage of dimeric tether **1** *versus* monomer **9**

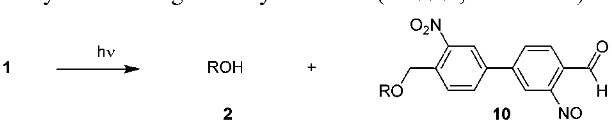




Entry	ROH		Yield ROH from monomer **9**	Yield ROH from dimer **1**
1		**2a**	66%[a], [b]	>99%[a], [b]
2	n-$C_{16}H_{33}OH$	**2b**	78%[a], [b]	>99%[a], [b]
3	n-PrOH	**2c**	40%[a], [d]	60%[a], [d](78%)[c], [d]
4		**2d**	71%[a], [d]	72%[a], [d](98%)[c], [d]
5	BnOH	**2e**	40%[a], [d]	59%[a], [d](99%)[c], [d]

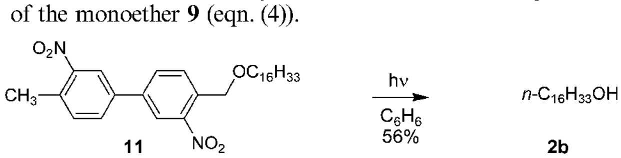
[a] 0.018 M in deoxygenated benzene, λ_{max} = 350 nm. [b] Isolated yield. [c] 0.018 M in deoxygenated dioxane, λ_{max} = 350 nm. [d] Deuterated solvent was used, yield determined by ^{1}H NMR integration with an internal standard.

alcohols. For this reason, the reaction yields were determined by ^{1}H NMR integration of the crude reaction mixture in the presence of an internal standard. For the photolysis of ethers **1c–e** in benzene, sub-quantitative yields of recovered alcohols were observed (59–72%). However, signals corresponding to unreacted *o*-nitrobenzyl ethers were not evident in the NMR spectra. We postulated that the lower yields were due to precipitation of the monoreacted nitrosobenzaldehyde **10** (eqn. (3)), which would sequester one equivalent of unreacted ether.‡ To combat precipitation of the partially reacted linker, the photolyses of diethers **1c–e** were performed on dioxane solutions. Upon irradiation of dipropyl ether **1c**, dicyclohexyl ether **1d** and dibenzyl ether **1e** dissolved in dioxane-d$_8$, no precipitate was observed and the yields were significantly enhanced (78–99%, entries 3–5).



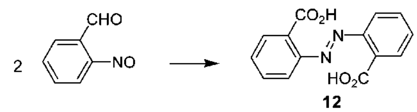
(3)

One possible explanation for the higher yields of alcohol recovered from photolysis of the diether **1** *vis-à-vis* monoether **9** is the difference in the electronics of the two ring systems. However, UV spectra of the two starting materials are nearly identical in the wavelength range of irradiation (see ESI†). Additionally, photolysis of the monoether **11** which possesses a nearly identical ring system to the diether **1** leads to a yield of alcohol that is analogous to that of the monoether **9** (eqn. (4)).



(4)

Previous reports on the use of the *o*-nitrobenzyl protecting group have proposed that dimerization and rearrangement of the *o*-nitrosobenzaldehyde by-product affords diazobenzene **12** which results in a reduction of reaction yield because of competitive absorption by **12** (eqn. (5)).[10] For the photolysis of our biaryl diether **1**, the by-product **3** is highly insoluble; thus, precipitation may prevent the formation of side-products that would interfere with the desired photolytic reaction. In support of this hypothesis, the ^{1}H NMR spectrum of the crude mixture obtained upon photolysis of diether **1** displays a very broad signal in the aromatic region indicative of aggregate formation. In contrast, the spectrum of the crude material following photolysis of monoether **9** displays multiple peaks in the aromatic region from numerous aromatic side-products.



(5)

In conclusion, we have prepared a new dimeric bis(*o*-nitrobenzyl) diether linker that can be photolyzed at two positions to release two equivalents of primary, secondary, or benzylic alcohol in good to excellent yields. This provides a general means of holding two masked functional groups in close proximity until light triggers their release.

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Notes and references

‡ Precipitate formation was observed for all photolyses performed on benzene solutions, with the exception of bis(dodecyl) ether **1b**. The high yields of recovered alcohols **2a** and **2b** indicate that, in those two cases, the precipitate is the nitrosobenzaldehyde by-product **3** (see eqn. (1)).

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